Remarks

Claims 2-4 are pending.

By the above amendment, claim 1 has been canceled. Claim 2 has been rewritten to be in independent form and to more clearly define the chain Ii degradant product as previously recited in claim 4. Claim 3 has been amended to enhance clarity. Claim 4 has been amended to provide further coverage for the method useful in a clinical trial setting (i.e., where the subject is a human), as supported in the original specification, e.g., at page 4, line 12.

In the outstanding Office Action, the Examiner required a new declaration because the originally submitted declaration was signed but not dated by the inventors. Accordingly, Applicants submit herewith a substitute declaration fully executed by the inventors.

The Examiner also rejected claims 1-4 under 35 U.S.C. § 112, second paragraph, for indefiniteness. With respect to the Examiner's point that "the subject treated" lacked antecedent basis, Applicants have amended claim 2 to provide clear antecedent basis for "the subject." Regarding the Examiner's comment that step b) of claim 1 was vague and not clearly correlated, this basis for rejection has been rendered moot by the cancellation of claim 1. Although Applicants disagree with the Examiner's assertion that the antecedent basis in each of the preambles of dependent claims 2-4 was unclear, Applicants have provided an equivalent preamble that more explicitly follows the preamble terminology of the independent claim. Concerning the Examiner's position that original claim 2 was indefinite in defining how its steps relate to those of claim 1, the

cancellation of claim 1 has obviated this ground of rejection. Finally, claim 3 has been amended to use the well-known terminology in place of the originally recited acronym "ELISA" (see, e.g., WO 99/58153, page 14, line 25) as suggested by the Examiner. In view of the foregoing, the rejection for indefiniteness should be withdrawn.

Claims 1-4 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Chapman et al. (WO 99/58153) in view of Willmann et al. (US 6,495,333). The Examiner indicated that the Chapman et al. reference discloses a method for monitoring the effect *in vivo* of a cathepsin S inhibitor by detecting the presence of invariant chain Ii on the surface of a cell. The Examiner also argued that Example III of this reference discloses the evaluation of the effects of cathepsin S inhibitors on Ii degradation by obtaining a cell sample of splenocytes, lysing the cells, and then analyzing the lysates for the accumulation of an approximately 10 kDa fragment of Ii (i.e., pI0Ii). The Examiner noted that the claimed method differs from the Chapman et al. method in employing a blood sample. The Examiner applied the Willmann et al. reference as supposedly suggesting the detection of p10Ii as taught by Chapman et al. using peripheral blood samples as taught by Willmann et al., because the secondary reference recognizes the difficulty in studying function in dendritic cells because of their rarity but shows ease in collecting blood as opposed to lymphatic tissue, and achieves the goal of non-invasive procedures in monitoring compound activity for pharmaceutical evaluation studies of autoimmune disorders such as in the method of Chapman et al. This rejection is respectfully traversed.

Example III of Chapman et al. describes experimental methodology for analyzing the effects of cathepsin S activity on Ii chain degradation and MHC class II peptide loading using cathepsin S knockout mice to help establish the role of cathepsin S in Ii processing. Having shown that MHC class II complexes in splenocytes from -/- mice retain the p10Ii fragment, however, the methods described by Chapman et al. for monitoring the effects of cathepsin S inhibitors detect not the presence of the p10Ii fragment, but the presence or absence of the Ii chain, and not from a blood sample, but on a cell surface. See, e.g., Chapman et al., pages 13-14 and claims 35-51.

In an attempt to cure the deficiencies of the teachings of Chapman et al., the Examiner cited Willmann et al. as supposedly providing motivation for converting the cell-surface detection method of Chapman et al. to a blood-sample detection method. The Examiner, however, failed to explain why the artisan would have been motivated to modify the Chapman et al. compound evaluation or diagnostic methods to analyze whole cell lysates of purified white blood cells from a blood sample for the presence of the p10Ii fragment as in the claimed invention, rather than to detect the presence or absence of the Ii chain on a cell surface. The Willmann et al. reference discloses a flow cytometric method for measuring dendritic cell function in whole blood, not a method for monitoring the effect *in vivo* of a cathepsin S inhibitor administered to a subject, let alone of detecting a p10Ii fragment. Since the methods of the two references are for distinct types of assays, the artisan would not have been motivated to combine their teachings. And even assuming *arguendo* that the artisan were to have looked to the secondary reference,

there would have been no motivation to select and combine various aspects of its teachings with those of the primary reference so as to arrive at the claimed method.

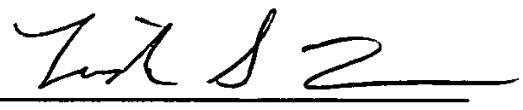
In summary, since the Section 103 rejection fails to explain why the person of ordinary skill in the art would have looked to the particular sources of information cited in hindsight by the Examiner, selected particular elements or teachings in them, and combined them in the way necessary to achieve the claimed invention, a *prima facie* case of obviousness has not been established. Consequently, the Section 103 rejection is in error and should be withdrawn.

As shown above, the pending claims are allowable. Accordingly, Applicants request prompt and favorable action.

Applicants also request the Examiner to initial the Forms PTO-1449 submitted with the Information Disclosure Statements dated November 26, 2001, and January 21, 2004, and return the initialed forms with the next official correspondence to confirm consideration of the cited references. Applicants acknowledge with appreciation the Examiner's return of the initialed Form PTO-1449 (Submission Under MPEP 609D) submitted with the Information Disclosure Statement dated February 25, 2002.

Respectfully submitted,

Date: June 25, 2004



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